Remarks

Reconsideration of this Application is respectfully requested. Upon entry of the foregoing amendment, claims 1, 2, 4-7, 9-13, 28-31 and 36-44 are pending in the application, with claims 1, 28 and 31 being the independent claims. Claims 3, 8, 14-27 and 32-35 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. New claims 36-44 are sought to be added. Support for the amendments to claims 1, 28 and 31 can be found, for example, in the specification as filed at page 16, paragraph 50. Support for addition of the recitation "cell permeable" in claims 1, 28 and 31 can be found in U.S. Patent No. 6,342,611, which corresponds to U.S. Appl. No. 09/168,888, which was incorporated by reference in Applicants' specification. See page 7, paragraph 18, and page 34, paragraph 104, last sentence.[1] Claim 28 has also been amended to correct a clear typographical error in the term "synergises." Support for new claims 36-44 can be found, for example, in original claims 4-7 and 9-13 respectively. These changes are believed to introduce no new matter, and their entry is respectfully requested. Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Summary of the Office Action

In response to Applicants' traversal of the Restriction Requirement, the Examiner has rejoined Group II with Group I, and has examined claims 1-31. The Examiner has

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[1]A copy of U.S. Patent 6,342,611 was submitted as Document AI3 in Applicants' Information Disclosure Statement filed May 10, 2002.

indicated that the first line of the specification should reflect the relationship of this application to U.S. provisional application no. 60/222,897, filed August 3, 2000. The Examiner has made two separate rejections under 35 U.S.C. § 112, first paragraph; a rejection under 35 U.S.C. § 112, second paragraph; a rejection under 35 U.S.C. § 102(b); and four rejections under 35 U.S.C. § 103(a).

Objections to the Specification

The Examiner indicates that "Applicant should amend the first line of the specification to reflect the relationship between the instant application and provisional application 60/222,897 filed August 3, 2000 stated on the oath." Office Action, page 2, section 6. Applicants have amended the specification such that the first line reflects this relationship.

Rejections under 35 U.S.C. § 112, first paragraph

Enablement

Claims 1-31 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly "**does not** reasonably provide enablement for any methods for identifying any immunosuppressive agent as set forth in claims 1-31 using any reporter compound having any measurable property which is responsive to any caspase cascade. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims." Office Action, page 3, section 9, lines 24-28 (emphasis in original). Applicants traverse this rejection.

Solely to expedite prosecution and not in acquiescence to the rejection, claims 14-27 are cancelled. Hence, this rejection is moot as it applies to claims 14-27.

The M.P.E.P. provides guidance to Examiners regarding examining claims for compliance with the enablement requirement:

> Before any analysis of enablement can occur, it is necessary for the examiner to construe the claims. For terms that are not well-known in the art, or for terms that could have more than one meaning, it is necessary that the examiner select the definition that he/she intends to use when examining the application, based on his/her understanding of what applicant intends it to mean, and explicitly set forth the meaning of the term and the scope of the claim when writing an Office action. See *Genentech v. Wellcome Foundation*, 29 F.3d 1555, 1563-64, 31 USPQ2d 1161, 1167-68 (Fed. Cir. 1994).
>
> In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure. A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

M.P.E.P. § 2164.04 (rev. 8th ed. Feb. 2003). Hence, after the claim has been properly construed, the Examiner must review the specification to ascertain whether it enables the full scope of the claim. Moreover, the specification must be taken as enabling unless the Examiner establishes a reasonable basis to question the enablement.

The Examiner has apparently misconstrued the claims as being directed to use of "any reporter compound." *See* Office Action, page 3, section 9, line 25. In contrast to

this incorrect claim construction, the claims were limited to a method using "a reporter compound having at least one measurable property which is responsive to the caspase cascade." Specification, original claim 1. Moreover, "reporter compounds" are apparently misconstrued by the examiner to include "a fluorogenic or fluorescent reporter compound such as rhodamine 110 having the structure as shown in formula VII on page 17 linked to a caspase or an enzyme involved in the intracellular apoptosis cascade. . . ." Office Action, page 4, lines 5-7. Applicants respectfully assert that the reporter compounds useful in the claimed method are not linked to a caspase or enzyme involved in the intracellular apoptosis cascade. Applicants' specification describes the reporter compounds as comprising "an amino acid sequence, which may be recognized *by* any of the intracellular proteases or peptidases that are produced as a result of caspase cascade activation." Specification, page 15, paragraph 49, first two sentences. Hence, Applicants' claimed methods employ reporter compounds having a peptide substrate, *not a caspase or enzyme involved in the intracellular apoptosis cascade.*

Besides misconstruing the claims, Applicants believe that the Examiner has not set forth a *prima facie* case that the specification does not enable the claims as originally drafted. The Examiner's allegation that the specification does not enable the claimed invention is not supported by any extrinsic evidence or sound scientific reasoning. Rather, the Examiner maintains the lack of enablement rejection upon the basis of an irrelevant reference which allegedly teaches "that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the . . . [conformation] of the protein. . . ." Office Action, page 4, lines 20-21. As stated above, Applicants' claimed method employs reporter compounds having a

peptide substrate, *not a caspase or enzyme involved in the intracellular apoptosis cascade*. Hence, the Examiner has not established a *prima facie* case that the claims are not enabled.

However, solely to expedite prosecution and not in acquiescence to the rejection, Applicants have amended claims 1, 28 and 31 such that they are directed to a method employing a cell permeable reporter compound having at least one measurable property which is responsive to the caspase cascade, wherein the reporter compound comprises (i) a caspase substrate; and (ii) a fluorogenic or fluorescent moiety, whereby said at least one measurable property is a change in fluorescence. Applicants' specification enables the full scope of these claims. *See, e.g.* Specification page 15, paragraph 49. Moreover, the claimed method requires living cells. The claims specifically state that the cells be "viable." Claims 1, 28 and 31.

Applicants are not required to exhaustively provide experimental guidance for every potential reporter molecule. Rather, the USPTO has promulgated guidelines explicitly stating that

> [f]or a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

M.P.E.P. §2164.02 (rev. 8th ed. Feb. 2003). Applicants respectfully assert that the Examiner has not set forth a *prima facie* case that the claimed genus of reporter compounds are not enabled by the specification. However, solely to expedite prosecution, and not in acquiescence to any rejection, Applicants refer the Examiner to

the '611 patent which is fully incorporated by reference. In particular, the '611 patent tabulates multiple substrates that can be used for multiple caspases in reporter compounds. Column 10, line 56 to column 11, line 45.

In view of the amendments and remarks above, Applicants respectfully submit that the rejection under 35 U.S.C. § 112, first paragraph for lack of enablement has been rendered moot. Applicants respectfully request that the examiner reconsider and withdraw this rejection.

Written Description

Claims 1-31 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The specification does not reasonably provide a **written description** of *any* reporter compound having *any* one measurable property, which is responsive to any caspase cascade." Office Action, page 5, section 10, lines 1-6 (emphasis in original). Applicants traverse this rejection.

The M.P.E.P. provides guidance to Examiners regarding examining claims for compliance with the written description requirement:

> A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 USPQ at 97.

M.P.E.P. § 2163.04 (rev. 8th ed. Feb. 2003). Hence, the Examiner must provide a reasonable basis from which to assert that Applicants' claims are not supported by an adequate written description.

As with the enablement rejection discussed above, the Examiner has misconstrued the claims and applied irrelevant reasoning in support of the rejection. In contrast with the Examiner's allegations, the claims are not directed to a method employing any reporter compound having any measurable property. Moreover, the claims are limited to methods employing intact, viable cells.

The Examiner's reliance upon Regents of the University of California v. Eli Lilly & Co., 119 F3d 1559 (Fed. Cir. 1997, "*Regents*") is irrelevant. In *Regents*, the Federal Circuit held that

> a cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the DNA.

Regents at 1568-1569. Here, Applicants are claiming a method which employs a cell permeable reporter compound having at least one measurable property which is responsive to the caspase cascade, wherein said reporter compound comprises (i) a caspase substrate; and (ii) a fluorogenic or fluorescent moiety, whereby said at least one measurable property is a change in fluorescence. Applicants claims are not directed to and do not encompass any DNA which may encode the caspase substrate.

Moreover, referring to the PTO's promulgated Written Description Guidelines, the Federal Circuit in a recent decision stated

> [i]n its Guidelines, the PTO has determined that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure,

> other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Guidelines, 66 Fed. Reg. at 1106 . . . .

Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F3d 956 (Fed. Cir. 2002, "*Enzo*").

Here, Applicants written description clearly identifies a representative number of reporter compounds. Specification, page 16, paragraph 50 to page 18, paragraph 58, especially paragraph 58. Moreover, explicit reference is made to U.S. Patent Application Serial No. 09/168,888 (the '611 patent) which is wholly incorporated by reference. The '611 patent provides further written description of a large number of representative reporter compounds useful for Applicants' claimed method. *See, e.g.*, col. 10, line 41 to col. 11, line 45. The above cited portions of Applicants' specification gives more than a sufficiently detailed description of the reporter compounds, both with respect to useful fluorogenic moieties and caspase substrates. Their physical formula as well as their function have been provided and are apparent to the skilled artisan upon reading Applicants' specification.

Withdrawal of the rejections under 35 U.S.C. § 112 is respectfully requested.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-13 and 28-31 are rejected under 35 U.S.C. §112, second paragraph, as allegedly "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Office Action, page 6, section 12, lines 1-3. Applicants traverse this rejection.

However, solely to expedite prosecution and not in acquiescence to the rejection, Applicants have amended claims 1, 28 and 31 such that the rejection is now moot.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 102

Claims 1-11, 14-25 and 31 are rejected under 35 U.S.C. § 102(b) as being anticipated by Evans, D. L. *et al.*, "Differential Sensitivity to the Induction of Apoptosis by Cisplatin in Proliferating and Quiescent Immature Rat Thymocytes is Independent of the Levels of Drug Accumulation and DNA Adduct Formation," *Canc. Res. 54*: 1596-1603 (1994, "Evans *et al.*"). Applicants respectfully traverse this rejection.

Solely to expedite prosecution and not in acquiescence to the rejection, claims 1 and 31 have been amended to be directed to a method employing a cell permeable reporter compound comprising, *inter alia*, a caspase substrate. In the presence of a caspase protease, the reporter molecule is hydrolyzed and all or a portion of the caspase substrate is cleaved from the fluorogenic moiety. Specification, page 15, paragraph 49. Because the fluorogenic moiety fluoresces more strongly after the reporter molecule is hydrolyzed, the reporter molecules can be used to identify immunosuppressive agents according to the claimed method. *Id.*

In contrast, the method described by Evans *et al.* employs acridine orange (AO) or trypan blue (TB) to observe morphological changes to DNA. Evans *et al.*, page 1597, left column, "Assessment of Cell Viability;" page 1596, footnote 4; and page 1599, right column lines 26-28. Exhibits A and B are provided herewith and show the structures of these indicator dyes. Neither of these compounds are caspase substrates which undergo hydrolysis in the presence of a caspase protease.

The M.P.E.P. clearly enunciates that for a reference to anticipate a claim under 35 U.S.C. § 102(b), the reference must teach every element of the claim. M.P.E.P. § 2131 (rev. 8th ed. Feb. 2003). Here, Evans *et al.* fails to teach a reporter molecule comprising a caspase substrate. Hence, Evans *et al.* fails to teach every limitation of Applicants' claims 1 and 31.

Solely to expedite prosecution and not in acquiescence to the Examiner's rejection, claims 14-25 have been cancelled. The rejection of these claims under 35 U.S.C. § 102(b) is now believed to be moot.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the 35 U.S.C. § 102(b) rejection.

Rejections under 35 U.S.C. § 103(a)

First Rejection: Claims 1, 12, 14 and 26

Claims 1, 12, 14 and 26 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Evans *et al.* in view of Wesselborg, S. *et al.*, "Triggering via the alternative CD2 pathway induces apoptosis in activated human T lymphocytes," *Eur. J. Immunol.* 23: 2707-2710 (1993) ("Wesselborg *et al.*"); and Hug, H. *et al.*, "Rhodamine 110-Linked Amino Acids and Peptides as Substrates to Measure Caspase Activity upon Apoptosis Induction in Intact Cells," *Biochem. 38*: 13906-13911 (1999) ("Hug *et al.*"). Applicants respectfully traverse this rejection.

The Examiner bears the initial burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103. In particular, the M.P.E.P. sets forth the criteria necessary to satisfy this burden:

> To establish a *prima facie* case of obviousness, three basic criteria *must* be met. First, there *must* be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there *must* be a reasonable expectation of success. Finally, the prior art reference (or references when combined) *must* teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success *must* both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP § 2143 - § 2143.03 for decisions pertinent to each of these criteria.

M.P.E.P. § 2142 (rev. 8th ed. Feb. 2003, emphasis added). Applicants respectfully assert that the references cited in support of the 35 U.S.C. § 103 rejection do not meet these criteria, and that consequently the Examiner has not established a *prima facie* case of obviousness.

In regard to the first criteria, the Examiner has failed to provide any suggestion or motivation to modify or combine the three references. The Examiner apparently alleges that the skilled artisan would be motivated to combine Evans *et al.* with Wesselborg *et al.* and Hug *et al.* to arrive at the claimed invention

> because Wesselborg *et al* teach that apoptosis is cell type specific and antibody such as anti-CD3TcR monoclonal antibodies trigger apoptosis only in activated but not resting mature peripheral T cells (See abstract, in particular). Hug *et al* teach that it is difficult to detect apoptosis in vivo and ex vivo since the apoptotic cells are removed by cells with phagocytic activity and rhodamine 110 coupled to amino acids or peptides are capable of detecting caspase in early apoptosis; the reference reporter compound is more sensitive than conventional PhiPhiLux staining and capable of . . . [penetrating] the cell membrane (See page 13910, column 2, in particular). Evans *et al* teach that cell undergoing apoptosis is associated with activation of caspase which can be readily distinguishable from the number of viable

> cells since the latter displayed diffuse nuclear staining patterns (See page 1597, Assessment of Cell Viability, in particular).

Office Action, page 8, line 26 to page 9, line 4. This statement, however, does not refer to any suggestion or motivation found within the references to modify or combine the reference teachings. Furthermore, this statement is not an explanation as to why the skilled artisan would modify the disclosure of Evans *et al.* with the disclosures of Wesselborg *et al.* and/or Hug *et al.* to arrive at Applicants' claimed invention. Rather, the Examiner's statement merely lists the alleged teachings of each of these references. Absent a motivation or suggestion to combine reference teachings, the examiner has improperly relied upon hindsight reasoning in combining references in support of the rejection under 35 U.S.C. § 103(a). *Cf.* M.P.E.P. §§ 2142 and 2143 (rev. 8th ed. Feb. 2003).

Even if there were a proper suggestion or motivation for combining these three references, any combined teachings could not satisfy the third criteria for setting forth a *prima facie* case of obviousness. As discussed above, the Examiner has relied upon an erroneous understanding of Applicants' claims. See Applicants' comments above regarding the enablement rejection. In addition, among other limitations, *none* of the references teach or suggest calculating a first ratio and identifying potential immunosuppressive agents as recited in part (g) of Claim 1. Accordingly, the Examiner has not satisfied the third criteria necessary in setting forth a *prima facie* case of obviousness.

Solely to expedite prosecution and not in acquiescence to the Examiner's rejection, claims 14 and 26 have been cancelled. The rejection of these claims under 35 U.S.C. § 103(a) is now believed to be moot.

Because a *prima facie* case of obviousness has not been set forth, Applicants respectfully request that the Examiner reconsider and withdraw this rejection under 35 U.S.C. § 103(a).

Second Rejection: Claims 1, 2, 13-15 and 27

Claims 1, 2, 13-15 and 27 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Evans *et al.* in view of Zeher, M. et al., "Correlation of Increased Susceptibility to Apoptosis of CD4+ T Cells with Lymphocyte Activation and Activity of Disease in Patients with Primary Sjögren's Sydrome," *Arthritis & Rheumatism*, *42*:1673-1681 (1999, "Zeher *et al.*); and Hug *et al.* Applicants traverse the rejection.

The Examiner has failed to satisfy the criteria necessary (discussed above at "***First Rejection: Claims 1, 12, 14 and 26***") to set forth a *prima facie* case of obviousness. In particular, the Examiner has relied upon an erroneous understanding of Applicants' claims. In addition, the Examiner has failed to provide any suggestion or motivation to modify or combine the three references. The Examiner apparently alleges that the skilled artisan would be motivated to combine Evans *et al.* with Zeher *et al.* and Hug *et al.* to arrive at the claimed invention

> because Zeher *et al* teach that there is a positive correlation between the increased susceptibility to apoptosis of peripheral CD4+ T cells and activity of disease from patient with Sjogren's syndrome compared with resting T cells from healthy tissue that is not afflicted with the immunopathological symptoms (See abstract, in particular). Hug *et al* teach that it is difficult to detect apoptosis in vivo and ex vivo since the apoptotic cells are removed by cells with phagocytic activity and rhodamine 110 coupled to amino acids or peptides are capable of detecting caspase in early apoptosis; the reference reporter compound is more sensitive than conventional PhiPhiLux staining and capable of . . . [penetrating] the cell membrane (See page 13910, column 2, in particular). Evans *et al* teach that cell undergoing apoptosis is associated with activation of caspase which can be readily distinguishable from the number of viable cells since the later displayed diffuse nuclear staining patterns (See page 1597, Assessment of Cell Viability, in particular).

Office Action, page 10, lines 6-17. This statement, however, does not refer to any suggestion or motivation found within the references to modify or combine the reference teachings. Furthermore, this statement is not an explanation as to why the skilled artisan would modify the disclosure of Evans *et al.* with the disclosures of Zeher *et al.* and/or Hug *et al.* to arrive at Applicants' claimed invention. Rather, the Examiner's statement merely lists the alleged teachings of each of these references. Absent a motivation or suggestion to combine reference teachings, the examiner has improperly relied upon hindsight reasoning in combining references in support of the rejection under 35 U.S.C. § 103(a). *Cf.* M.P.E.P. §§ 2142 and 2143 (rev. 8th ed. Feb. 2003).

Even if there were a proper suggestion or motivation for combining these three references, any combined teachings could not satisfy the third criteria for setting forth a *prima facie* case of obviousness. In particular, among other limitations, *none* of the references teach or suggest calculating a first ratio thereby identifying potential immunosuppressive agents as recited in part (g) of Claim 1. Accordingly, the Examiner has not satisfied the third criteria necessary in setting forth a *prima facie* case of obviousness.

Solely to expedite prosecution and not in acquiescence to the Examiner's rejection, claims 14, 15 and 27 have been cancelled. The rejection of these claims under 35 U.S.C. § 103(a) is now believed to be moot.

Because a *prima facie* case of obviousness has not been set forth, Applicants respectfully request that the Examiner reconsider and withdraw this rejection under 35 U.S.C. § 103(a).

Third Rejection: Claims 28-30

Claims 28-30 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Evans *et al.* in view of Migita, K. *et al.*, "FK506 Potentiates Steroid-Induced T-Cell Apoptosis," *Transplantation*, 64: 1365-1369 (1997, "Migita *et al.*"); and Hug *et al.* Applicants traverse the rejection.

The Examiner has failed to satisfy the criteria necessary (discussed above at "***First Rejection: Claims 1, 12, 14 and 26***") to set forth a *prima facie* case of obviousness. In particular, the Examiner has relied upon an erroneous understanding of Applicants' claimed invention. In addition, the Examiner has failed to provide any suggestion or motivation to modify or combine the three references. The Examiner apparently alleges that the skilled artisan would be motivated to combine Evans *et al.* with Migita *et al.* and Hug *et al.* to arrive at the claimed invention

> because Migita *et al* teach that exposing activated T cells to a combination of known immunosuppressive compounds can determine the synergistic effects of said compounds (See abstract, in particular). Hug *et al* teach that it is difficult to detect apoptosis in vivo and ex vivo since the apoptotic cells are removed by cells with phagocytic activity. However, rhodamine 110 coupled to caspase amino acids or peptides substrate is capable of detecting caspase in early apoptosis; the reference reporter compound is more sensitive than conventional PhiPhiLux staining and capable of . . . [penetrating] the cell membrane (See page 13910, column 2, in particular). Evans *et al* teach that cell undergoing apoptosis is associated with activation of caspase which can be readily distinguishable from the number of viable cells since the latter displayed diffuse nuclear staining patterns (See page 1597, Assessment of Cell Viability, in particular). Evans et al further teach that plurality of populations of viable cultured active T cells can be culture[d] in separate wells of a microtiter plate such as 96-wells immunoassay plates (See page 1598, column 1, first paragraph, in particular).

Office Action, page 11, line 30 to page 12, line 11. This statement, however, does not refer to any suggestion or motivation found within the references to modify or combine the reference teachings. Furthermore, this statement is not an explanation as to why the

skilled artisan would modify the disclosure of Evans *et al.* with the disclosures of Migita *et al.* and/or Hug *et al.* to arrive at Applicants' claimed invention. Rather, the Examiner's statement merely lists the alleged teachings of each of these references. Absent a motivation or suggestion to combine reference teachings, the examiner has improperly relied upon hindsight reasoning in combining references in support of the rejection under 35 U.S.C. § 103(a). *Cf.* M.P.E.P. §§ 2142 and 2143 (rev. 8th ed. Feb. 2003).

Even if there were a proper suggestion or motivation for combining these three references, any combined teachings could not satisfy the third criteria for setting forth a *prima facie* case of obviousness. In particular, among other limitations, *none* of the references teach or suggest calculating a ratio thereby identifying compounds which synergise with known immunosuppressants as an activator of the caspase cascade, as recited in part (h) of Claim 28. Accordingly, the Examiner has not satisfied the third criteria necessary in setting forth a *prima facie* case of obviousness.

Because a *prima facie* case of obviousness has not been set forth, Applicants respectfully request that the Examiner reconsider and withdraw this rejection under 35 U.S.C. § 103(a).

Fourth Rejection: Claims 14-17 and 22

Claims 14-17 and 22 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Evans *et al.* in view of Lesage, S. *et al.*, "$CD4^+CD8^+$ Thymocytes Are Preferentially Induced to Die Following CD45 Cross-linking, Through a Novel Apoptotic Pathway," *The Journal of Immunology, 159*: 4762-4771 (1997, "Lesage *et al.*"); and Bradbury, D. A., *et al.*, "Measurement of the ADP:ATP ratio in human leukaemic cell lines can be used as an indicator of cell viability, necrosis and apoptosis," *Journal of Immunological*

Methods 240: 79-92 (2000, "Bradbury *et al.*"). Applicants traverse this rejection. However, solely to expedite prosecution and not in acquiescence of the rejection, these claims have been cancelled. Accordingly, Applicants believe that this rejection is now moot.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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